

Serial No.: 09/620,586
Amendment dated November 1, 2004
Reply to Office Action of June 30, 2004

REMARKS

1. Claims

Claims 1-16, 18-23, 29 and 53-64 are currently pending. Applicant has included a set of the pending claims. No amendments have been made except that in limited cases, the status of the claim (previously presented, currently amended, etc.) has been updated.

2. Rejections under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-2, 16, 19-23, 29, 53-54, 56, 58 and 60-64 under 35 U.S.C. §103(a) as being unpatentable over Barker et al. (U.S. Patent No. 6,369,201) in view of the known facts disclosed in the Specification at page 16, lines 24-30 and newly cited WO 95/05849 for the reasons set forth in the previous Office Action. Barker has been cited for disclosing a method for *in vivo* down-regulation of myostatin activity, which will result in an increase in the muscle mass of an animal, which comprises administering at least one full length myostatin polypeptide, or at least one myostatin analogue, wherein myostatin is derived from bovine and myostatin immunoconjugate comprising at least one myostatin polypeptide linked to an immunological carrier. The Examiner further notes that the Barker reference teaches the modification of myostatin to include a vaccine composition comprising the myostatin polypeptide or analogue formulated with various adjuvants, such as aluminum, and "immunological carriers" such as the *Tetanus toxoid* epitope. Finally, the Examiner argues that Barker teaches that the association of the myostatin molecule with the *Tetanus toxoid* epitope can be used to facilitate the breaking of auto-tolerance. The newly cited WO 95/05849 reference ("Mouritsen") discloses a method for down-regulating self-proteins by immunizing with analogues of the self-proteins wherein a number of the amino-acid sequences have been substituted with a corresponding number of amino acid sequence which comprises a foreign T-helper epitope, such as *Tetanus toxoid*, while maintaining the overall tertiary structure of the self-protein in the analogue. Based on the combined teachings of the references and the statement on

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page 16 of Applicant's disclosure, the Examiner concludes that it would have been "obvious, conventional and within the skill of a person of ordinary skill in the art at the time the invention was made *to identify the exact position for substitution of the *Tetanus toxoid epitope* in the *myostatin molecule* in order to facilitates breaking autotolerance of said molecule and to apply the teaching of the known fact disclosed in the Specification on page 16, lines 24-30 and WO '849 to those of U.S. Patent '201 to obtain the claimed method . . .*" (emphasis added). Applicant respectfully traverses.

First, Applicant notes that the Examiner has "considered" the Declaration of Dr. Steen Klysner submitted with Applicant's last response but was not persuaded that the claimed invention was non-obvious. Dr. Klysner, unquestionably a person of ordinary skill in the art, testified that, in his opinion, a person of ordinary skill in the art could not determine the exact positions of the myostatin molecule which could be modified to insert a foreign T-helper epitope without engaging in undue experimentation. Instead of according this testimony its due weight, the Examiner states that he "disagrees with the Applicant's statement that for a person of ordinary skill in the art it would not been obvious to determine the exact position for substitution of the *Tetanus toxoid epitope* in the *myostatin peptide* in order to facilitate the breaking of auto-tolerance." In support of his position, the Examiner again points to the generic disclosure on page 16, lines 24-30 of the Specification and the teachings of Mouritsen which generally teach that foreign T-helper epitopes (such as the *Tetanus toxoid epitope*) can be inserted into self-proteins to facilitate the breaking of auto-tolerance and argues that only routine experimentation would be required to identify the exact position for substitution of the *Tetanus toxoid epitope* within the myostatin molecule. Applicant submits that none of the references cited by the Examiner provide the teachings necessary to enable the skilled artisan to determine the exact positions for substitution while maintaining (1) the overall secondary, tertiary and quaternary structure of the peptide and (2) a substantial portion of the self-proteins B-cell epitopes.

The Examiner is reminded that conclusory statements of similarity or motivation, without any articulated rationale or evidentiary support, do not constitute factual findings. MPEP 2144.08. To support an obviousness rejection, the Examiner must establish that (1) there was some suggestion or motivation, either in the references themselves or in the knowledge generally

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available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (2) there was a reasonable expectation of success and (3) that the prior art references when combined would teach or suggest all of the claim limitations. Applicant submits that the Examiner has not established a *prima facie* case of obvious but instead has engaged in impermissible hindsight and obvious to try reasoning to reject the claimed invention as obvious over the prior art.

It is axiomatic that the teaching or suggestion to make the claimed combination and the reasonable expectation for success must both be found in the prior art, not in applicant's disclosure. (emphasis added) *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In the present case, Applicant has identified the exact positions of the myostatin molecule which can be modified by substituting a foreign T-helper epitope without destroying the antigenic and immunogenic properties of the polypeptide (i.e. by maintaining the secondary, tertiary and quaternary structure of the peptide, preserving a substantial fraction of the self-peptide B-cell epitopes, etc.). As detailed in the Declaration of Dr. Klysner, the exact positions for inserting a foreign T-helper epitope were only determined after considerable experimentation and a series of complex sequence and structure analysis were performed. It should also be emphasized that the modified polypeptides had to satisfy a number of criteria before they could be characterized as "suitable immunogens". In particular, the present inventors had to ensure that the modified polypeptides or variants:

- A) Could be expressed from a transformed cell in amounts sufficient to render the use of the variant feasible;
- B) Could be obtained as a pure product. In other words, that effective purification and (optionally) refolding can be provided;
- C) Retained a substantial portion of the B-cell epitopes from the wild-type protein;
- D) Contained a minimal number of epitopes that could potentially cross-react with other self-proteins; and

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E) Provided for the relevant immune response (it should be capable of interfering with the activity of myostatin, or alternatively, be capable of clearing myostatin to such a high degree that an effect on muscle mass is observed).

Thus, the development of the present invention was not mere "routine" experimentation. Modifying peptides or creating suitable immunogenic peptides is not an exact or predictable science. In order to determine that all of the aforementioned criteria were met, the inventors had to screen a large number of candidates molecules, identify which portions of the myostatin peptide could be modified and identify where foreign T-helper epitopes could be inserted without destroying the native B-cell epitopes or destroying the secondary, tertiary and quaternary structure of the polypeptide. If one were to accept the Examiner's position, then arguably the existence of a known molecule and the technology of combinatorial chemistry would render obvious all variants of the known molecule which are obtained through combinatorial chemistry. This would be a decidedly contrary and erroneous result especially in view of the limited and generic teachings of the cited prior art references.

The Examiner has conceded that Barker fails to disclose inserting a P2 or P30 *Tetanus toxoid* epitope into the myostatin polypeptide or, indeed, where such modifications could be made. In fact, the Examiner, on page 4 of the Office Action, admits that the Barker reference does not explicitly teach the particular modification of myostatin. As noted in Applicant's prior response, Barker only discloses a method for in-vivo down-regulation of myostatin and the linking of an "immunological carrier", such as tetanus to a myostatin molecule, it does not teach modifying a myostatin molecule by inserting a foreign T-helper cell epitope such as the P2 or P30 *Tetanus toxoid* epitope. The only portion of the Barker reference which discusses preparing modified myostatin molecules merely relates to performing amino acid deletions, substitution and/or additions while maintaining a certain percent identity with the native polypeptide (see generally cols. 6-7 of Barker). This in no way suggests that foreign T-helper epitopes could be inserted into defined portions of the myostatin polypeptide. The disclosure on p. 16, lines 24-30 of the Specification merely states that there are several art-recognized ways of modifying a peptide self-antigen to facilitate the breaking of auto-tolerance, including introducing at least one foreign T-helper epitope into the peptide. This general concept is echoed in the Mouritsen

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reference which describes inducing antibody responses against self-proteins with the aid of foreign T-cell epitopes. However, none of these references in any way disclose or suggest that modifications could be made in the specific portions of the myostatin peptide identified by the inventors of the present application.

With respect to the Mouritsen reference, Applicant agrees that the Mouritsen reference describes creating modified self-proteins by introducing foreign T-cell epitopes. However, Applicant would point out that this reference is arguably more general in nature than e.g. the Barker reference as it is directed to producing TNF-alpha or ubiquitin mutants, not modified myostatin molecules. And, while it describes the importance of inducing minimal changes to the highly conserved self-protein ubiquitin, as well as in TNF-alpha (see pages 6-7 of Mouristten), the reference contains absolutely no guidance with respect to modifying a myostatin molecule so as to preserve its overall secondary, tertiary and quaternary structure and maintain a substantial fraction of the wild-type myostatin B-cell epitopes. Therefore, Applicant submits that the relevance and applicability of this reference is extremely limited. However, it is clear that the skilled artisan would not be able to extrapolate the general teachings of the Mouritsen reference to arrive at the present invention.

Despite these deficiencies, the Examiner continues to argue that the skilled artisan would be able to deduce exactly where modifications (i.e. the insertion of foreign T-helper cell epitopes) could be made in the myostatin molecule without destroying its immunogenicity. In other words, the Examiner has determined that Applicant's claimed invention is obvious in view of the general teaching in the prior art which points vaguely but not specifically to the claimed invention. In doing so, the Examiner has applied the impermissible "obvious to try" and "hindsight" standards.

Applicant has not disputed that the introduction of foreign T-cell epitopes in self-peptides could be used to facilitate the breaking of auto-tolerance. Indeed, this is what is noted in the Specification. However, Applicant submits that the Examiner has failed to identify a single reference which discloses or suggests where a foreign T-helper cell epitope, such as the *Tetanus toxoid* epitope, can be introduced into a myostatin molecule such that the modified peptide

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satisfies the criteria set forth above and would be useful in the practice of the claimed method. The Examiner merely argues that it would be well within the skill of the ordinary artisan or that it would involve routine experimentation to identify the exact positions of the myostatin molecule which could be modified. This is clearly a case where the improper "obvious to try" rationale has been applied wherein "what would have been obvious to try would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful . . . MPEP 2145 citing *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Unlike the situation in *O'Farrell*, and as detailed above, there is no prior publication which provides the detailed enabling methodology, the suggestion to modify the prior art to produce the claimed invention and evidence suggesting that the modification would be successful. Instead, the Examiner has used the Applicant's own teachings and success in determining the exact positions for substitution against him and argued that other similarly skilled artisans could accomplish the same task without engaging in undue experimentation. While it may be true that the prior art suggested that self-proteins could be modified by inserting a foreign T-cell epitope, (i.e. that it might be obvious to try), there is no reasonable expectation that such a modification would produce a suitable immunogen (as defined above). In other words, a person of ordinary skill in the art would not have a reasonable expectation of success of producing modified myostatin molecules which satisfied the criteria set forth above. In such a case, there simply can be no finding of obviousness. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd. and Genetics Institute, Inc.*, 927 F.2d 1200 (Fed. Cir. 1994).

In view of the foregoing remarks, it is clear that the teachings in the prior art would not enable the skilled artisan to identify the exact positions for modification described in the present application. Applicant submits that the present invention is, in no way, suggested or rendered obvious in view of the Barker reference, the general disclosure on page 16 of the present application or the Mouritsen reference, either singly or in combination. As such, Applicant respectfully requests reconsideration and removal of the obviousness rejection.

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Examination on the merits and favorable action and allowance of all the claims are requested.

If the Examiner has any questions concerning this application, he is requested to contact Leonard Svensson (Reg. No.: 30,330) the undersigned at (714) 708-8555 in California.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicant hereby petition for an extension of one (1) months to October 30, 2004 (Saturday), for the period in which to file a response to the Office Action dated June 30, 2004. The amount of \$110.00 is to be charged to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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